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Can Lyme disease manifest and progress differently in children? - a review

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ABSTRACT

One of the most common zoonoses in humans and the most well-known tick-borne disease—Lyme disease—affects many body systems. Spirochetes of the genus *Borrelia* affect the skin, which is the portal of infection, and then the joints, cardiac system, and nervous system, which gives a wide range of symptoms that make up one disease. The study aims to present the state of knowledge about the disease and the differences in its course in children. The pathognomonic symptom is erythema migrans, appearing after a tick bite, but it does not occur in all infected people. Its presence is the basis for diagnosis and initiation of treatment. In the case of the presence of others, the diagnosis should be two-stage and consist of the detection of specific antibodies using the enzyme immunoassay method and the Western blot technique. The disease is widely known and often overdiagnosed due to some non-specific symptoms. The article, through a literature review, discusses issues related to the disease, its symptoms, diagnosis, and treatment, paying particular attention to the pediatric population. Starting treatment at an early stage (involving the skin) is very important because, in the vast majority of cases, we can prevent disease progression to the disseminated stage and the resulting complications. In younger patients, spirochete infection is not so rare and may have a different clinical course. For this reason, it requires in-depth diagnostics, as the symptoms may resemble other childhood diseases.

Keywords: Lyme disease, borreliosis, neuroborreliosis, pediatric population, infectious disease

1. INTRODUCTION

The history of spirochete pallidum as a disease accompanying humanity goes back much earlier than we may think, namely several thousand years ago. The spirochete genetic material found in the body of a 5,300-year-old mummy found

in the Alps over a quarter of a century ago (Keller et al., 2012). It coexisted unnoticed with humans and other species until 1977. When the first cases of arthritis associated with tick bites were noticed in Lyme. Five years later, Willy Burgdorfer discovered the culprit that caused the symptoms of the disease and named it *Borrelia burgdorferi*, and the disease itself - Lyme disease. The most common spirochetes include *B. garinii* and *B. afzelii*, which predominate in Europe, and *B. burgdorferi*, which is more common in the USA, but at least ten species cause Lyme disease in humans.

There are relationships between individual types of spirochetes and their affinity for specific organs. *Borrelia burgdorferi* infection is associated with arthritis and neurological symptoms, *Borrelia garinii* most often affects the nervous system, and *Borrelia afzelii* usually causes late skin lesions (chronic atrophic dermatitis of the extremities). The highest incidence of Lyme disease occurs in the northeastern states of the USA, Central Europe, Scandinavia, and Russia. The endemic occurrence of the disease in these areas is related to the habitats of ticks. Although the disease has been known for years, its diagnosis is sometimes difficult due to unusual symptoms or overlapping stages, as it is a rigid division and not always so clear when translated to the patient.

Aim of the study

This work aims to review the literature to show the state of knowledge and to search for information about the clinical differences of Lyme disease in children and adults, as well as the diagnostic and treatment differences. Through this study, the authors would like to pay attention to a frequently occurring disease, however non-specific, among children, who are particularly vulnerable due to outdoor play. Knowing the differences allows for the isolation of this disease during diagnosis, which will have a positive impact on the treatment process for patients.

2. METHODOLOGY

While working on the article, we searched medical databases such as PubMed and Google Scholar, taking keywords as a criterion. We also took into account the consistency of the topic and the type of diseases described. We compared the knowledge with chapters on Lyme disease in scientific books. To search for various cases of Lyme disease in the population of children and adults, we extended the time criterion to more than ten years ago. To find relevant articles, the phrases: "Lyme disease", "treatment of borreliosis", "diagnostics of neuroborreliosis", "pediatric population", and "infectious disease" were used.

3. RESULTS AND DISCUSSION

Description of the state of knowledge

Lyme disease is a multi-system disease, whose symptoms affect the skin, central nervous system, heart, eyes, and joints. General symptoms such as malaise, headaches, muscle pain, weakness, and fever may be the first manifestation of the disease. The most characteristic symptom of this affliction is erythema migrans; Lyme disease may also manifest as cutaneous pseudolymphoma, chronic atrophic dermatitis, neuroborreliosis, arthritis, myocarditis, and ocular Lyme disease (Stanek et al., 2011). Conventionally, the duration of the disease is divided into three stages: Early Lyme disease, early disseminated Lyme disease, and late Lyme disease. The most characteristic sign of the first stage is erythema migrans, but general symptoms may also occur up to several weeks after infection (Wilking and Stark, 2014).

The second stage means spreading the disease and the spirochetes reaching the nervous system, heart, eyesight, and joints. The third stage is associated with persistent infection manifesting after months or years and symptoms affecting the skin, joints, and nervous system. Classic erythema migrans is the most common clinical manifestation of Lyme disease, but it is the first symptom in only 30% of patients. It means invasion of spirochetes in the skin. A clinically significant lesion is a ring with a diameter of ≥ 5 cm and a transparent center that appears 3 to 30 days after the tick bite (Tibbles and Edlow, 2007). The migration process of spirochetes sometimes lasts only 17 hours after the tick bite, but usually, this transmission occurs after 72 hours. Tick saliva contains ingredients that disrupt the immune response at the bite site, making infection much more accessible.

Immunosuppressive proteins in tick saliva interfere with both specific and nonspecific immune responses. In patients untreated in the first phase of the disease, within a few days or weeks after infection, spirochetes spread via blood circulation and the occurrence of systemic symptoms in the skeletal and articular system, nervous system, heart, and eyes. The most common symptom of late Lyme disease, developing months or years after infection, is arthritis and chronic atrophic dermatitis, affecting the distal parts of the limbs

and causing asymmetric skin discoloration. The lesions are bluish-red, accompanied by inflammatory swelling, the skin is thin, tissue-paper-like, and hairless (Gajewski et al., 2021; Lenormand et al., 2016).

Patients often report pain due to peripheral neuropathy. It occurs in 48-64% of patients with chronic atrophic dermatitis. Kristoferitsch et al., (1988) Another relatively rare cutaneous form of the disease is Lyme pseudolymphoma - it appears up to 2 months after infection in the area of the auricles, nipples, and scrotum. It appears as a painless red-purple lump (Maraspin et al., 2011). Arthritis occurs with recurrent exacerbations, during which painful swelling of the joint occurs, with abundant effusion in the joint cavity. Characteristically, there is no severe systemic inflammatory reaction and no fever. Large joints, from one to five (knees, ankles, elbows), are most often affected. Over time, flare-ups become less frequent (Gajewski et al., 2021). To be diagnosed with chronic arthritis, inflammation must persist in the same location for at least a year (Steere et al., 1994).

Involvement of the nervous system manifests itself as meningitis, paralysis of cranial nerves, and spinal nerve roots. The co-occurrence of erythema migrans occurs in 34-46% of patients (Rauer et al., 2020). Patients with meningitis complain of headaches, nausea, vomiting, fatigue, and photophobia. Inflammation of the cranial nerves most often manifests itself as facial nerve palsy. It is involved in >80% of cases, and in approximately 1/3 of cases, bilateral paralysis occurs (Moniuszko-Malinowska et al., 2021). In most cases, it disappears without complications, but in 5-10% of patients, it may remain a persistent paralysis (Kowalski et al., 2011). Radiculitis is characterized by severe neuralgia worsening at night, paresthesia, and muscle weakness; it more often affects the limb on which erythema migrans or a tick bite occurs.

The co-occurrence of meningitis and paralysis of cranial and peripheral nerves creates a triad called Bannwarth syndrome. The central nervous system, in rare cases, becomes inflamed, causing psychotic syndromes, dementia, cognitive impairment, spastic paralysis, sphincter paralysis, and quadriplegia (Kaiser, 1994). Encephalitis may lead to organic changes in the brain. Due to vasculitis, ischemia or hemorrhagic modifications may occur in the brain tissue (Zajkowska et al., 2015). Cardiac symptoms appear in the early disseminated form of Lyme disease in approximately five percent of patients. They occur in the form of myocarditis, manifested by atrioventricular block and other conduction disorders. It most often affects young adults and middle-aged men (Forrester et al., 2014). There are also known cases of ocular Lyme disease, which results in inflammation of the eye and optic nerve. However, due to the rarity of Lyme disease, it is recommended to exclude other medical conditions.

Diagnostics

Clinical symptoms are crucial in diagnosing Lyme disease, as their presence is an obligatory criterion for diagnosis. A positive laboratory test result does not entitle us to make a diagnosis, as it indicates contact with spirochetes in the past and is not an indication for treatment, the introduction of which could bring more negative effects and complications of antibiotic therapy rather than positive ones. To make a diagnosis and start treatment, the presence of clinical symptoms and positive laboratory test results are required. The only exception is the presence of erythema migrans, that allows us to make the diagnosis without performing additional tests. Laboratory diagnosis of Lyme disease is a two-step process: First, we perform serological tests detecting IgM and IgG antibodies.

Specific antibodies are detected in serum by enzyme-linked immunosorbent assays (ELISA), chemiluminescent CLIA assays, or multiplexed MMIA assays. A negative result indicates a low probability of Lyme disease and the search for the causes of clinical symptoms elsewhere. A positive or doubtful result requires confirmation by Western blot, and then the outcome of this test will allow for the diagnosis. The mentioned first-stage methods - ELISA, CLIA, and MMIA - are characterized by highly sensitivity, while the Western blot method has high specificity (Kmieciak et al., 2016). The methods presented have their time limitations because specific IgM antibodies appear 3-4 weeks after infection and disappear after about half a year; IgG antibodies appear later, after 6-8 weeks, and may persist for many years.

If neuroborreliosis is suspected, antibodies are measured not only from the serum but also from the cerebrospinal fluid, which allows us to determine whether there is an infection of the central nervous system. Intradural antibodies form within 2 to 6 weeks of the onset of the disease (Moniuszko-Malinowska et al., 2023). It is recommended that blood collection and lumbar puncture at the same time. General examination of the cerebrospinal fluid shows lymphocytic pleocytosis and increased protein concentration. Calculating the index of cerebrospinal fluid concerning serum, which uses the concentration of antibodies and albumin, allows the diagnosis of neuroborreliosis to be classified as possible, probable, and inevitable (Kaiser, 1998).

Differences in children

Lyme borreliosis in children may have a different course and symptoms than in adults. Many of the symptoms are similar to other childhood diseases. Spinal nerve root inflammation and atrophic dermatitis are usually absent in children. The diagnosis of Lyme disease in children is much more difficult due to the variety of clinical symptoms and the rarity of diagnosis. The diagnostics and therapeutic procedures do not differ from those in adults, with a few exceptions. It is also more difficult to distinguish individual stages of the disease due to the immaturity of the immune system, especially in younger children. Characteristic symptoms of the second stage - early disseminated - appear earlier, often while skin lesions are present. In turn, the third, late phase and its symptoms appear sporadically or do not occur. Erythema migrans, as in adults, is also the most common symptom in children - it occurs in 77-89% of children with a symptomatic form of the disease.

However, its location may be different because in children, due to their shorter height, erythema is most often located on the head, neck, and behind the ears. In contrast, in adults and older children, location is on the limbs and trunk. It usually appears as a single lesion, but may also present as erythema with satellite, smaller lesions around the primary lesion (Fingerle and Huppertz, 2007). Lyme pseudolymphoma, although rare, occurs more often in children than in adults, and arises as a result of the spread of spirochetes and the activation of B lymphocytes that increase in response to circulating antigens. It appears in specific locations, is painless, and circumscribed, with a soft consistency and bluish-red color (Amschler et al., 2013). As in adults, the presence of erythema does not require confirmation of the diagnosis with serological tests and antibodies against *B. burgdorferi* should not be screened, because they occur in approximately five percent of healthy children living in endemic areas, which may give false positive results (Dehnert et al., 2012).

The clinical course of neuroborreliosis in children is often different than in adults. Lyme neuroborreliosis occurs in children mainly as meningitis, usually with a mild or subacute course, manifested by headache, coexisting with erythema migrans, or as isolated facial nerve palsy, including Bell's palsy (Esposito et al., 2013). When we are dealing with bilateral facial nerve palsy, the most common cause is Lyme disease. The most common symptoms of neuroborreliosis in the pediatric group are facial nerve palsy, headaches, weakness, neck stiffness, nausea, and fever (Skogman et al., 2012). Examination of the cerebrospinal fluid reveals lymphocytes, plasma cells, monocytes (cytosis up to several hundred), increased protein concentration, and intrathecal synthesis of specific IgM antibodies. The diagnosis requires serological diagnosis, cerebrospinal fluid examination results, and, above all, the presence of clinical symptoms.

Lyme arthritis in children affects large joints, usually the knees. It manifests itself with swelling, pain, and redness. It is often confused with juvenile arthritis, and it is important to remember the distinction between these diseases. Arthritis without treatment can become chronic and lead to cartilage and bone erosion, synovial hypertrophy, and fiber deposition. The guidelines recommend four weeks of antibiotic therapy, and if symptoms persist, repeat treatment. According to recommendations, it is possible to repeat this treatment but no more than two to three times (Parada-Turska, 2013).

Features of spirochetal involvement of the circulatory system observed in young patients include sudden cardiac arrhythmias, conduction disorders, and pericarditis or myocarditis. Cardiac symptoms appear simultaneously with erythema migrans or shortly after its occurrence. Lyme disease of the eye is very rare and manifests itself as uveitis, inflammation of the iris, or cornea. It occurs in children but requires a thorough differential diagnosis. The differences described are included in the table below (Table 1).

Table 1 Comparison of symptoms in adults and children

Population group Symptoms	Adults	Children
Erythema migrans (EM)	Erythema most often in the bitten area	Most often located on the head, neck, and behind the ears
Borrelial lymphocytoma (BL)	Inflammatory skin lesion that appears weeks to 2 months after infection, very rarely in adults	Lesion located on the auricles, scrotum or nipples - occurs more often in children
Acrodermatitis chronica atrophicans (ACA)	Bluish-red lesions, located mainly on the distal parts of the limbs, often in adults	Very rarely in children
Neuroborreliosis	In adults, mainly meningitis, paralysis of cranial nerves	In children, mainly meningitis and facial

	and/or spinal nerve roots; rarely encephalitis, myelitis; very rarely cerebral vasculitis;	nerve palsy
Lyme arthritis (LA)	One or several large joints	Large joints, usually the knees
Lyme carditis (LC)	Acute onset of atrioventricular conduction disorders (blocks I–III), arrhythmias, myocarditis	Cardiac arrhythmias, conduction disorders, and pericarditis or myocarditis
Ocular borreliosis	Conjunctivitis, uveitis, episcleritis, keratitis individual cases	

Treatment

Treatment involves the use of antibiotics active against *B. burgdorferi*. The first-line antibiotics in all forms of Lyme disease are doxycycline, amoxicillin, and cefuroxime axetil. If there are contraindications to the use of doxycycline, such as for those under eight years of age, as well as in cases of intolerance and contraindications to using other antibiotics of choice, azithromycin is used. *Borrelia* occurs intracellularly and crosses the blood-brain barrier, which causes problems during treatment (only some antibiotics cross the blood-brain barrier and only some elements intracellularly). Stages of disseminated Lyme disease, such as meningitis in the course of neuroborreliosis or myocarditis, require intravenous antibiotic therapy with ceftriaxone or cefotaxime. Effective treatment duration is 10–21 days, but should not last longer than four weeks.

Even weekly doxycycline therapy for erythema migrans is effective (Stupica et al., 2023). In the case of isolated facial nerve palsy and the absence of changes in the cerebrospinal fluid, suspect Lyme disease and administer doxycycline. Even in adequately treated patients, post-Lyme syndrome may occur, in which patients most often report bone and joint pain, chronic fatigue syndrome, and headaches. It is generally accepted that these symptoms are the result of permanent tissue damage by spirochetes or an immune reaction against them. There is currently no evidence to link these symptoms with active infection (Karlsson et al., 1990). In such cases, symptomatic treatment is indicated, as there is no evidence that repeated antibiotic therapy has health benefits and the resulting improvement in quality of life, which is associated with a significant risk of side effects, which research supports (Kaplan et al., 2003; Krupp et al., 2003).

4. CONCLUSION

Lyme borreliosis is a multisystem disease whose symptoms require differentiation from many other diseases, creating diagnostic difficulties. A tick bite may or may not occur at the time of the first symptoms of the disease; many patients don't remember the moment of a bite by a tick. However, even then, it should not be ruled out. The disease is seemingly benign and does not require complicated initial treatment. Still, in several percent of cases, it results in serious, multi-organ, severe complications that patients, both children and adults, have to deal with for a long time of their lives.

Therefore, it is essential to recognize it early and implement appropriate antibiotic therapy, which will allow for a cure in 90% of cases. In children, the prognosis for recovery is more favorable than in adults. Treating the disease at an early stage causes it to rarely progress into a chronic infection. This is different in adults, where we have more cases of particularly Lyme arthritis, which occurs in about 1/3 of patients with Lyme disease. Finally, we should emphasize that appropriate prevention is equally essential when staying in endemic areas - body protection, use of repellents in children over two years of age, and early removal of ticks. In many cases, these actions will help prevent contact with ticks and infection.

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Author's Contribution

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Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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